A prospective study of adverse drug reactions in hospitalized children

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Aims There are few publications of adverse drug reactions (ADRs) among paediatric patients, though ADR incidence is usually stated to be higher during the first year of life and in male patients. We have carried out a prospective study to assess the extent, pattern and profile risk for ADRs in hospitalized patients between 1 and 24 months of age.

Methods An intensive events monitoring scheme was used. A total of 512 successive admissions to two medical paediatric wards (47 beds) were analysed. The hospital records were screened daily during two periods (summer, 105 days and winter, 99 days), and adverse clinical events observed were recorded.

Results A total of 282 events were detected; of these, 112 were considered to be manifestations of ADRs. The cumulative incidence was 16.6%, no differences being observed between periods. Although there were no differences between patients under and over 12 months of age, risk was found to be significantly higher among girls compared with boys (RR = 1.66, 95% CI 1.03–2.52). The gastro-intestinal system was most frequently affected. The therapeutic group most commonly implicated was anti-infective drugs and vaccines (41.5%). The ADRs were mild or moderate in over 90% of cases. A consistent relationship was noted between the number of drugs administered and the incidence of ADRs.

Conclusions Hospitalized patients exhibited an ADR risk profile that included female sex and the number of drugs administered. No particular age predisposition was observed. The most commonly prescribed drugs are those most often implicated in ADRs in paediatric patients.

Keywords: adverse drug reactions, hospitalized children, paediatric patients

Introduction

Since children are not habitually involved in precommercialization clinical trials the information available upon launching a new drug on the market is limited. Hence it is important to apply postcommercialization vigilance systems to this group of patients [1, 2].

Although no specific confirmation is found in the literature, it is usually stated that the incidence of adverse drug reactions (ADRs) is higher during the first year of life, although only objective manifestations of ADR can be recorded in very young children. This conclusion is attributed to the physiological immaturity of patients in this age group [3, 4]. On analysing the data from voluntary reports, an increased frequency of notifications is observed for males under the age of 5 years and for females after this age [5, 6].

There have been few publications of ADRs among paediatric patients, and most reports involve isolated clinical cases [7]. Nevertheless, a number of studies do provide specific follow-up data. Incidences of 0.75–9.8% of all treated patients have been reported in the outpatient setting [8–11], compared with 2–4.3% of children hospitalized because of ADRs [12, 13]. Although few ADR studies involving hospitalized paediatric patients have been conducted, data have been published from the Boston Collaborative Drug Surveillance Program and from a study conducted in Granada (Spain) in 1989 by Vázquez de la Villa *et al.* [14, 15]. However, these studies comprise a patient age range of 0–18 years, with the reporting of global results that contribute little to elucidate circunstances in the first 2 years of life.

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Based on the hypothesis that patients 1 year of age or younger are at greater risk of developing ADRs; ADRs are more frequent in males up to the age of 5 years; and the most frequently used pharmacological groups are also those most often implicated in the appearance of ADRs, we carried out a prospective intensive events monitoring scheme and record of events to assess the extent, pattern and the profile risk for suffering an ADR in hospitalized patients between 1 and 24 months of age. A medication use study was also conducted.

Methods

The study was carried out in the Hospital Infantil Universitario La Fe in Valencia (Spain). This hospital has 291 beds and covers a population of 700 000, of which 15 000 are children 2 years old or younger. Successive admissions to two medical paediatric wards (Lactants B and Isolation Ward 2) were monitored.

The admissions evaluated corresponded to the use of 47 beds during two different periods, summer (105 days) and winter (99 days). Patients 1–24 months old with a hospitalization period of at least 24 h were included in the study. Repeat admission of the same patient was counted as two admissions when separated by an interval of at least 1 month. Oncological patients and those with HIV infection were excluded.

The methods have been described previously [13]. Briefly, during the study periods, the hospital records of all admitted patients were screened by one of the authors (MGL, a paediatrician). Data were recorded using a structured questionnaire designed *ad hoc* and including sociodemographic and anthropometric information, personal and family medical history, cause of admission and main clinical data. Questions regarding previous drug use were obtained by interview with parents, relatives, home nurses or others, as necessary. By visiting the wards daily, examining medical and nursing records and attending clinical rounds, details were recorded on drug orders, excluding intravenous fluid, oxygen, and blood products, and adverse clinical events that occurred during the hospitalization. When necessary, information was elicited from the ward nurses and prescribing physicians. All patients were followed-up until hospital discharge, in order to ascertain the final diagnosis.

An event was defined as any new clinical experience on the part of the patient not related to the admission diagnosis—regardless of whether or not it was considered medicine-related—including investigations and transfer to another ward. Event registers offer the advantage that, with full reporting, they include adverse reactions not recognized as such by the clinician; in contrast, they have the inconvenience that the data are crowded with a good deal of extraneous material. Adverse events not attributed to therapy are also noted in order to identify clinical occurrences which might constitute unrecognized ADRs. An adverse drug reaction is one that is noxious and unintended, and occurs at doses used in humans for prophylaxis, diagnosis, therapy, or modification of physiologic functions. Thus, this definition excluded therapeutic failures, poisonings, and intentional overdoses [16].

The clinical charts of patients were evaluated at joint meetings to select those cases of suspected ADR. The evaluation followed a two-dimensional scheme: (i) the temporal relationship between drug intake and a subsequent adverse event, and (ii) the role of the latter as a cause of a suspected ADR. Details on those patients in whom drug therapy was thought to have contributed in any way to a suspected ADR were documented using the spontaneous reporting system of the Regional Drug Surveillance Center maintained by the Spanish Drug Surveillance Scheme of the Spanish health authorities (Ministerio de Sanidad y Consumo).

The procedures involved in the reporting system and the assessment of the data have been described previously [5, 17, 18]. Briefly, in order to validate the cases, for every adverse effect reported efforts are made to collect the maximum amount of information on patient characteristics (sex, age, medical history, underlying diseases, etc.), drug treatment (suspected drug, dosage, route of administration, indication, date of beginning and stopping therapy, concomitant drugs, etc.) and characteristics of the adverse event (date of onset, clinical details, etc.). Once the case was validated, an imputability score was obtained from the algorithm utilized in the Spanish Drug Surveillance Scheme [13, 17], based on the successive evaluation of five criteria where each possesses several degrees, and which provides grades for the causal association between drug and adverse event.

The clinical manifestations experienced by the patients were classified according to the Adverse Reaction Terminology of the WHO [19]. A reactions profile was made by calculating the number of reports of each system-organ class of reaction as a percentage of all the reports. The reactions profile was graphically represented as a histogram. Severity was classified into four categories according to the Spanish Drug Surveillance Scheme: fatal, severe (directly life-threatening), moderate and mild [13]. The suspected drugs were classified according to the Anatomical-Therapeutic-Chemical classification (ATC) of the Norwegian Medicinal Depot [20].

All data from questionnaires and medical records were coded for subsequent analysis. The statistical analysis used the Student's *t*-test with a significance level of $P<0.05$. Comparisons of proportions were made using Chi-squared tests with the results expressed as relative risk (RR) and 95% confidence intervals. A linear regression

model was used for calculating the β coefficient of the relation between the number of drugs and the cumulative incidence of ADR.

Results

During the two study periods 512 admissions affecting 490 different children were included. Table 1 shows the distribution of patients admitted in the two study periods; the admissions were more numerous in winter, but there were similar numbers of males and females in both periods. There were no statistical differences between the two periods in terms of age, weight, height or length of stay in hospital (Table 1). In 354 admissions the patients were younger than 1 years and in the 158 they were older. The observational period comprises 3788 patient-days. The highest proportions of patients studied were from the emergency room ($n=415$, 81%) and from paediatric intensive care ($n=71$, 13.7%). The rest were from several medical paediatric units ($n=26$, 5.3%). Of the total of 512 admissions, there were three patients who had three separate admissions and 16 who had two separate admissions. The patients admitted had a wide variety of diseases, but 21 (4.3%) were thought to be due to an ADR [13]. Of the 512 patients hospitalized, 409 received drugs during hospitalization.

Events during hospitalization

During the study period 282 events were detected among 155 patients (1.8 event per patient). Among the 282 events detected, 112 were considered clinical manifestations of suspected ADR (39.7% of events). The nature of the rest of the events included varying clinical manifestations (110, 39%); transfer to other wards (35, 12.4%); laboratory changes (18, 6.4%); investigations (5, 1.8%); and surgical interventions (2, 0.7%).

Incidence of ADR during hospitalization

Of the 409 admitted patients who received drugs (150 admissions in the first period and 259 in the second), 59 (14.4%) had a suspected ADR to at least one drug during their stay in hospital. Two of the patients who suffered reactions to drugs during hospitalization had been admitted for a suspected ADR. One patient suffered three suspected ADRs, seven had two reactions, and the rest suffered one suspected ADR. There were no events which might have been mistaken for ADRs in the 103 patients (20%) who did not receive drugs. Thus, the cumulative incidence of ADR during hospitalization was 16.6%.

Table 2 shows the characteristics of patients who developed suspected ADR in both hospitalization periods. During the summer period there were 29 suspected ADRs (cumulative incidence 19.0%) while in the winter period there were 39 ADRs (cumulative incidence 15.1%). There was no statistical differences between the two periods in terms of age and weight. Likewise, there were no significant differences between children hospitalized in summer and children hospitalized in winter and between children older and younger than 1 year for ADRs suffered (RR = 1.28; 95% CI 0.83–1.99 and RR = 1.05; 95% CI 0.65–1.69, respectively). However, there were significant differences between sexes: girls had between 1.03 and 2.5 times the risk of developing an ADR compared with boys (RR = 1.61; 95% CI 1.03–2.52).

The mean length of stay in hospital of patients who developed suspected ADR was 12.1 days (s.d. = 9.6 days; range 2–48 days). The mean duration of hospital stay for patients who developed no reaction in the study was 7.4 days (s.d. = 6.2 days; range 1–44 days). The duration of stay of patients with reactions was on average 4.66 days longer than for patients without ADR (95% CI 2.09–7.23; $P<0.0005$).

Nature of adverse drug reactions

Figure 1 summarizes the suspected ADRs detected during both periods of hospitalization according to the organ-system affected. It should be noted that a single report can contain several clinical manifestations. During the first period the total number of clinical manifestation terms coded was 50, with a mean of 1.7 per ADR. In the second period, 62 clinical manifestations were coded,

Table 1 Patient characteristics and length of hospital stay (mean ± s.d.), in the two study periods.

	Sex	*Number of patients*	*Age (months)*	*Weight (kg)*	*Height (cm)*	*Length of stay (days)*
1st period	Male	93	9.7 ± 6.6	8.0 ± 3.0	70.4 ± 11.5	6.9 ± 6.3
(21–06/03–10–92)	Female	89	9.7 ± 7.1	7.2 ± 2.5	68.5 ± 10.5	7.2 ± 5.1
2nd period	Male	156	8.2 ± 5.9	7.5 ± 2.5	66.1 ± 11.2	6.9 ± 5.7
(10–01/27–04–93)	Female	174	8.4 ± 6.6	7.0 ± 2.6	66.9 ± 10.5	8.3 ± 7.9
Total	Male	249	8.7 ± 6.2	7.7 ± 2.7	68.6 ± 10.5	6.9 ± 5.9
	Female	263	8.8 ± 6.8	7.1 ± 2.6	67.0 ± 11.0	7.9 ± 7.0

Table 2 Characteristics of patients with suspected ADR during hospitalization, and number of patients (mean ± s.d.) in the two study periods.

	Sex	*Number of patients*	*Number of suspected ADRs*	*Age (months)*	*Weight (kg)*
1st period	Male	7	9	6.9 ± 4.8	6.5 ± 2.5
	Female	17	20	8.9 ± 7.7	6.9 ± 2.6
2nd period	Male	15	17	8.6 ± 7.2	8.5 ± 3.1
	Female	20	22	10.7 ± 7.2	8.2 ± 3.0

Table 3 Details of suspected adverse drug reactions classified as severe and fatal.

Age (months)	*Sex*	*Indication*	*Suspected drugs (*)in combination (fixed proportions)*	*ADR effects*	*Imputability*	*Severity*
12.6	Male	Convulsions	Diazepam	Apnoea	Probable	Severe
2.65	Female	Convulsions	Diazepam	Respiratory depression	Probable	Severe
14.8	Female	Diabetes mellitus	Human isophane insulin; Human regular insulin	Hypoglycaemia	Probable	Severe
3.64	Female	Disorders in urea metabolism	Sodium benzoate; Pyridoxine	Worsening of pathology; dyspnoea; heart failure; cardiac arrest	Improbable	Fatal
5.03	Male		Tetracosactrin	Bronchitis; enteritis; digestive candidiasis, necrotizing stomatitis	Possible	Fatal

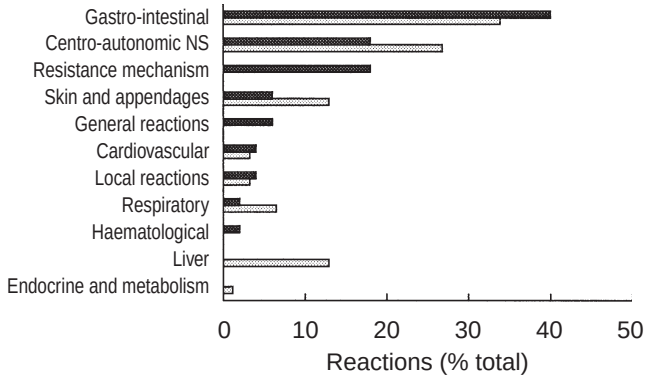

Figure 1 Profiles of the proportion of the total number of suspected adverse drug reactions for each of the major organ-systems distributed by periods of time (■ summer, ▨ winter). Note that a single admission can have several clinical manifestations.

with a mean of 1.6 per ADR. The most commonly affected organ-systems were the digestive system (36.6%), the central nervous system (22.3%), skin and appendages (9.8%), resistance mechanisms (8.0%) and liver (7.1%). Together, they accounted for 83.9% of all suspected ADRs. In addition, Figure 1 shows the different profiles in the two study periods: while in summer the second most commonly affected organ-systems were the central nervous system and resistance mechanism (18.0% each), in the winter it was the central nervous system (26.8%). Moreover, ADRs affecting the liver were only observed during the winter period (12.9%). In both study periods 49 different clinical manifestations were detected, of which 8 were coincident. The most common clinical manifestation of ADR during both periods was diarrhoea, with 9 cases in the summer period and 11 in the second; 3 cases of rash were detected in the summer period and 8 in the second; vomiting was recorded in 4 and 5 cases, respectively; somnolence was present in 4 and 3 cases in the summer and winter periods, respectively; and gastrointestinal candidiasis was observed in 5 cases during the summer period only.

Drugs causing adverse reactions

The 102 drugs suspected, alone or in combination, of causing ADR are shown in Figure 2, according to the ATC classification. In the summer 41 drugs were implicated compared with 61 in the winter. Comparing the two study periods, the therapeutic groups most commonly associated with suspected ADRs in both periods were Group J, which includes anti-infective agents and vaccines (45.1%), and Group N, which includes analgesics and anticonvulsive drugs (23.5%), followed by Group R (respiratory: 14.7%) and Group C (cardiovascular: 6.9%). However, some differences between periods were observed in the profile of drugs implicated in suspected ADR. Thus, while in the summer period the third therapeutic Groups were A (digestive system and metabolism) and C (cardiovascular) ($n = 4$; 9.8%, each), in winter the third therapeutic group was

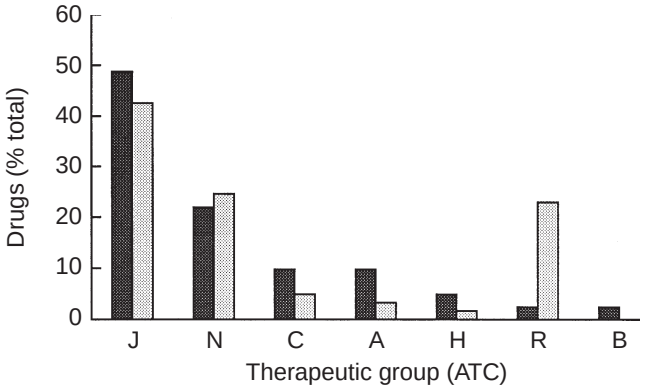

Figure 2 Profiles of the proportion of the total number of suspected adverse drug reactions for each therapeutic group distributed by periods of time (■ summer, ▨ winter). Note that a single admission can have several suspected drugs. J = anti-infective agents, including vaccines; N = central nervous system, including analgesics; C = cardiovascular; A = digestive system, including vitamins; H = hormones; R = respiratory system; B = blood and haematopoietic organs

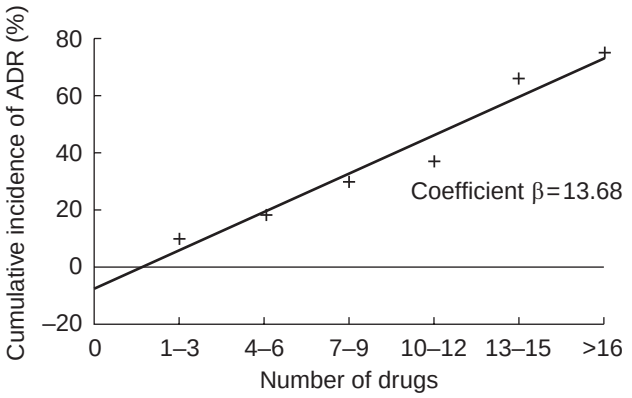

Figure 3 Regression line between cumulative incidence of ADR and the number of drugs administered.

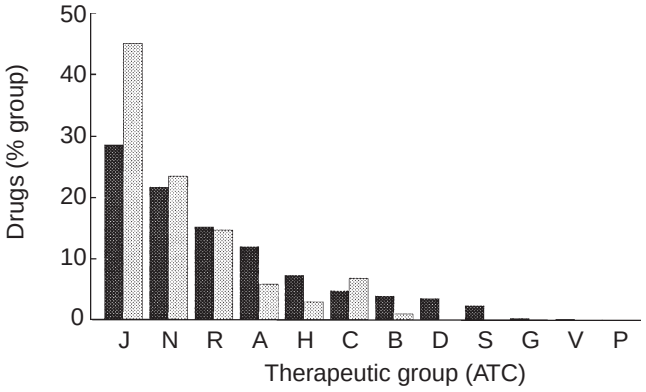

Figure 4 Profiles of the proportion of the total number of used drugs (■) and implicated (▨) in suspected adverse drug reactions for each therapeutic group. J = anti-infective agents, including vaccines; N = central nervous system, including analgesics; R = respiratory system; A = digestive system, including vitamins; H = hormones; C = cardiovascular; B = blood and haematopoietic organs; D = dermatologic; S = sensory organs; G = genitourinary therapy, including sex hormones; V = Various; P = antiparasitic drugs.

respiratory drugs ($n = 14$; 23.0%). The most common ADR-related pharmaceutical formulation was amoxycillin-clavulanic acid, observed in 9 and 10 cases in each period, respectively, followed by valproic acid in the summer period (related to 4 cases of suspected ADR) and amoxycillin and fenoterol (5 cases each) in the winter period. During the winter we also recorded 4 cases of suspected ADR related to diazepam and 4 to phenobarbitone.

The mean number of pharmaceutical formulations consumed during the study period for suspected ADR was 5.2 ± 4.5 per patient, significantly different from the number consumed by patients who did not suffer ADR (2.9 ± 2.1). The patients with ADR consumed an average of 2.3 drugs more than those without ADR (95% CI 1.00–3.60; $P < 0.005$), and a consistent relation was noted between the number of drugs administered and the cumulative incidence of ADR, which increased from 9.71% per patient receiving only one drug to 75% per patient receiving more than 16 drugs, with a slope of 13.68 (Figure 3). Of the 1325 pharmacological formulations used in the hospital, 102 were implicated in suspected ADR. Figure 4 shows the relations between the most commonly used drugs and the drugs implicated in suspected ADR.

Severity and probability grading of ADR

Suspected ADRs reported in hospitalized patients were of mild severity in 52.9% (36 cases), moderate in 39.7% (27 cases), severe in 4.4% (3 cases) and fatal in 2.9% (2 cases). Table 3 shows details of the five suspected ADRs classified as severe and fatal. Four of these are recognized reactions to the implicated drugs but the remaining ADR has not been previously documented. Except in the two fatal cases, all patients recovered without long-term sequelae. Regarding imputability, according to Spanish causality terms [17], the suspected ADRs were considered to be definite in 2 case (2.9%), probable in 51 (75%), possible in 11 (16.2%), conditional in 3 (4.4%) and improbable in 1 case (1.5%).

Discussion

Intensive monitoring of the admissions to 47 beds of a paediatric hospital has provided information on the follow-up of 3788 patient-days that comprised 512 admissions of 490 patients. The analysis of the sample shows that the distribution by sex was similar to that of the overall population. The age and anthropometric

characteristics at admission to hospital were similar in both sexes. In the present study the predominance of patients aged 1 year or younger coincided with the findings of a pilot study carried out in Boston [14] and the work of Whyte & Greenan [21] although those studies involved a larger population and included children over the age of 12 years.

More than the 30% of the hospitalized patients suffered some event during their stay in hospital. Of these events, 40% were related to the drugs administered in hospital and were considered as ADR. The incidence of ADR found in this survey (16.6%) is higher than that reported by Vázquez de la Villa *et al.* in Granada (Spain) involving a sample of similar size though with children 1–8 years older [15]. Whyte & Greenan [21] found that 6% of hospitalized patients had ADRs, but they included children up to and over the age of 12 years. These differences in the incidence of ADRs could be related to the different patient ages in those studies. Moreover, as commented by Skegg & Doll [22] and Kennedy *et al.* [23], the method used for intensive monitoring of events in the present study improves ADR detection, but detects many ADRs that are mild and self-limiting. On the other hand, although other authors also using the detection of events reported high percentages of ADR [14, 24, 25], they included patients up to age 16 years and oncology patients; consequently, the results described cannot be compared with our own. In a previous study [13] in paediatric outpatients who suffered ADRs as a cause of admission to a paediatric hospital, we observed a lower incidence (4.3%). This difference may be explained by the characteristics of drug therapy and the disturbances in general condition among hospitalized children.

We found the female sex was associated with slightly increased risks of suffering ADR. Other authors have reported no sex predisposition [15, 21], and the results also contrast with those obtained by Mann *et al.* [6] and Morales-Olivas *et al.* [26] through spontaneous reporting of ADRs. On the other hand, we found no particular age predisposition, in agreement with the study by Cirko-Begovic *et al.* [11] in infants and preschool outpatients. However, our results contrast with those obtained by Kramer *et al.* [8], who found that patients under the age of 1 year developed ADR more commonly than older patients. Nevertheless, their study involved general paediatric outpatients and a methodology different from our own.

The present results show different ADR profiles during the two study periods, but in agreement with other studies [8, 27], the digestive system was the organ most commonly affected followed by central nervous system in both periods. These two organ-systems affected coincide with the results described by Vázquez *et al.* [15], though in reverse order. Interestingly, ADRs due to an altered resistance mechanism—mainly candidiasis secondary to antibiotics—appeared only in summer. These differences between periods may be related to variations in both the characteristics of the pathology and to the patterns of drug utilization.

The therapeutic class most frequently implicated in suspected ADRs was antibiotics. However, their percentage involvement in ADRs is higher than their prevalence of use. In agreement with other studies carried out in ambulatory paediatric patients, this pharmacological group is followed by analgesics/antipyretics [8–11]. These therapeutic groups are the most commonly used in paediatric patients [4]. Drugs acting on the respiratory system appear more frequently implicated in ADRs during the winter. In contrast, Rylance *et al.* [28] observed a high prevalence of use of drugs acting on the respiratory system during the spring-summer period. These authors explain their finding in that allergic pathology is more frequent during this period of the year in outpatient children. Hence, it is possible that the treatment of these conditions is mainly in the community, thereby accounting for our observation of no major use of these drugs during summer. Differences such as those commented above emphasize the need to report the season in which the studies are made, along with the population studied. Our results during the winter period are similar to those described by Cirko-Begovic *et al.* [11], who reported information from January to April although in outpatients. As recommended by Lee *et al.* [29], it is not advisable to compare the patterns of drug utilization in different studies as the season in which the studies were made may not be specified, and the pattern of drug use differ considerably as a result.

Some 20% of the hospitalized patients did not request any medication. This may be explained, at least in part, by the large number of hospitalizations during the second period (winter) due to brochiolitis, the treatment of which consists of oxygen therapy. Whyte & Greenan [21] likewise found a large proportion of patients (26.7%) who received no pharmacological treatment—particularly in the younger patient groups. In agreement with the observations of most studies, drug consumption was restricted to a few therapeutic groups. Hence, antibiotics, analgesics, bronchodilators in winter, and surprisingly vitamins during summer were the most commonly used groups [4]. The lower proportion of vaccines may be due to a shorter hospital stay and/or to the fact that the patients were vaccinated out of the hospital. Our results are in conflict with those of Moreland *et al.* [30], who described a higher consumption of drugs acting on the central nervous system and a lesser proportion of patients who received pharmacological treatment. Changes in prescription habit over the last 15 years may explain the differences observed.

The mean number of drugs consumed per patient was low, and there were significant differences between the number consumed by patients with ADRs and those without ADRs. In agreement with the literature, where similar observations are reported [15, 21, 25], this result supports the hypothesis that ADR risk is higher in patients who concurrently receive several drugs. This hypothesis is reinforced by the observation of a clear relationship between the number of drugs consumed and the cumulative incidence of ADRs (coefficient $\beta = 13.68$).

ADR severity was found to be similar in both periods, although the two fatal cases occurred during the summer, and the cases classified as severe in the winter. Comparisons with other studies are not possible because possible differences in severity scales. The finding of diazepam was implicated in two cases classified as severe suggests that although the most commonly used drugs are most often implicated in ADRs, only a few drugs are actually implicated in severe ADRs. Although a high proportion of cases exhibited an apparent cause/effect relationship (75%), the lack of re-exposure made it impossible to make definite conclusions [17].

It is difficult to compare patterns of drug use and adverse reactions among the few paediatric studies published to date, though patterns of drug use and effects can be evaluated within a given study. In agreement with others authors, our patients with ADRs stayed in hospital significantly longer than those without reactions, and moreover received a greater total number of drugs. Only Hurtwitz [31] found no differences in the duration of hospital stay. Almost 50% of the ADRs detected in the present study were moderate or severe, thus requiring a change in drug therapy and/or a prolongation of hospital stay. Moreover, the stay in hospital and the number of drugs consumed may be considered, at least in part, as risk factors in the genesis of the ADRs in children, in agreement with other authors [15, 31–34].

Our results suggest that, in contrast to ADRs leading to hospital admission [13], hospitalized paediatric patients exhibit an ADR risk profile that includes the female sex and the number of drugs administered during hospitalization. The most commonly prescribed drugs are most often implicated in ADRs. The latter are costly and interventions to reduce their frequency can be justified economically as well as in terms of improvement in the quality of care [35].

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